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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Makoto INOUE et al.	Confirmation No.:	7683
Serial No.:	10/587,123	Art Unit:	1648
371(c) Date:	January 18, 2007	Examiner:	A. Boesen
Customer No.:	21559		
Title:	METHOD FOR PRODUCING VIRAL VECTORS		

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REPLY TO RESTRICTION REQUIREMENT

In reply to the Restriction Requirement that was mailed in connection with the above-captioned case on November 6, 2007, Applicants elect the invention of Group I, claims 1-10. The election is made with traverse.

As an initial matter, Applicants note that claims 2, 3, 27, and 28 have been amended in the concurrently filed Preliminary Amendment. The remarks set forth below, while directed to the claims as amended, also apply to the claims that were subject to the Restriction Requirement.

The Office states (page 2):

> [T]he special technical feature of the claimed invention is a modified virus and a viral vector which propagation depends on a cleavage of a viral protein by a protease, and the method of producing the said virus.

Applicants respectfully disagree.

Applicants submit that protease dependency is not limited to modified viruses and, therefore, is not the special technical feature defining the contribution which the presently claimed invention makes over the art[1]. Propagation of wild-type Sendai virus depends on cleavage of a viral protein by a protease, i.e., a trypsin-like protease. Therefore, a wild-type Sendai virus has the feature which the Office asserts to be the special technical feature. As explained below, Applicants submit that the presently claimed invention (claims 1-35) encompasses a special technical feature that defines a contribution over the art.

Claim 1 reads as follows.

> A method for producing a virus whose propagation depends on cleavage of a viral protein by a protease, wherein the method comprises the step of producing the virus in the presence of: (i) a modified viral protein in which a cleavage sequence for the protease is changed to a cleavage sequence for an alternative protease, and (ii) the alternative protease, and wherein the produced virus comprises the modified viral protein that is cleaved <u>but does not comprise a gene encoding the modified viral protein</u>. (Emphasis added.)

In contrast to a wild-type Sendai virus, the virus encompassed by the present claims is produced in the presence of a modified protein having a cleavage site for an

[1] Even if the Office asserts that the special technical feature of the claimed invention is a virus the propagation of which depends on a cleavage of a viral protein by a *different* protease than the protease which cleaves the wild-type protein, this still is not the special technical feature of the present invention for the reasons set forth herein.

alternative protease which is *different* from the protease which cleaves the wild-type protein. The produced virus does not have the gene encoding the modified protein. Such a virus is not described by the Inoue et al. (J. Virology 77(11):6419-6429, 2003; hereafter "Inoue et al.") reference cited by the Office. The claimed invention has a feature which the wild-type Sendai virus does not have (and which Inoue et al. do not describe) and this special technical feature is a contribution that the presently claimed invention makes over the prior art and links all pending claims.

In particular, Applicants note that the modified virus of claim 26 has the special technical feature recited above in relation to claim 1. Similarly, the non-propagating vector of claim 11 and the cell of claim 22 are important tools for making the modified virus of claim 26. Accordingly, all pending claims share the special technical feature.

The Office further states (pages 2 and 3):

> Inoue et al. (Journal of Virology, June 2003, Vol. 77, p. 6419-6429) disclose the special technical feature of the present invention in that they disclose the modified virus and a viral vector which propagation depends on a cleavage of a viral protein by a protease, and the method of producing the said virus (see the entire document).

Applicants, note that Inoue et al. use the word "protease" three times in the entire document. The first use is in the abstract, and the second and third uses are in column 1 of page 6428. The uses of "protease" in Inoue et al., for the following reasons, in no way anticipate the special technical feature that links the present claims to form a single general inventive concept.

With respect to the first use of "protease," Inoue et al. state (abstract, lines 6-8):

> Instead, SeV/ΔM infection brought about a significant increase of syncytium formation under conditions in which the fusion protein was proteolytically cleaved and activated by trypsin-like protease.

It is true that the fusion (F) protein of SeV/ΔM was cleaved and activated by a trypsin-like protease. However, this is no different from the wild-type virus; the wild-type Sendai virus is also activated by a trypsin-like protease. In the section titled "Recovery of M gene-deficient SeV from cDNA" (page 6420, col. 2), Inoue et al. state:

> Approximately 10^7 LLCMK2/F7/A cells that were expressing F protein after AxCANCre infection were suspended in MEM containing AraC (40 μg/ml) and trypsin (7.5 μg/ml), layered onto the transfected cells (18), and cultured at 37°C for an additional 48 h. (Emphasis added.)

Namely, SeV/ΔM was made by using a wild-type F protein, and therefore SeV/ΔM has the wild-type F protein. As shown in panels (A) and (C) of Figure 1 of Inoue et al., SeV/ΔM (SeV18+/ΔM-GFP) also has a wild-type F gene. As such, like a wild-type Sendai virus, SeV/ΔM has the wild-type F *gene and protein* which is cleaved and activated by a trypsin-like protease. Consequently, the SeV/ΔM virus does not contain the special technical feature of the present invention.

The second and third uses of "protease" are found in the discussion section of Inoue et al. Here the reference states (page 6428, col. 1, 1st full paragraph):

> Little or no such cell-to-cell spreading occurred in the absence of trypsin. This indicates that the cell-to-cell spreading of SeV/ΔM can be controlled by the activation of F protein by treatments such as the addition of trypsin-like proteases and suggests that further conversion of the cleavage site of F protein to recognition sequences for other proteases is possible. (Emphasis added.)

Inoue et al. describe that the cell-to-cell spreading of SeV/ΔM can be controlled by

the cleavage and activation of a wild-type F protein by trypsin-like proteases. In contrast, the special technical feature of the claimed invention is making a modified virus using an alternative protease than the protease which cleaves the wild-type protein, *where propagation of the produced viral vector does not depend on the alternative protease.* The alternative protease is involved in making the virus, but is not involved in propagation of the virus after infection. Inoue et al. do not teach this special technical feature.

For all the above reasons, Applicants submit that the claims of Groups I-III are linked by a single general inventive concept that provides a special technical feature (i.e., the produced virus does not have the gene encoding the modified protein) that makes a contribution over the prior art. Applicants respectfully request that the Office reconsider the present Restriction Requirement and rejoin Groups I-III.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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